Newer antidepressants in irritable bowel syndrome: what is the evidence?

Commentary on

Selective serotonin reuptake inhibitors for the management of irritable bowel syndrome: a meta-analysis of randomized controlled trials

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Irritable bowel syndrome (IBS) is a chronic unexplained condition characterized by abdominal discomfort or pain that is intimately linked to disturbed defecation; bloating is a common accompanying symptom [1, 2]. Specific symptom-based criteria have been identified for the syndrome, and a positive diagnosis is possible based on taking an adequate medical history [1-3]. Multiple deranged pathophysiological mechanisms have been identified in this condition, including abnormalities of gut transit and sensation, but whether the motility abnormalities arise primarily from within the gastrointestinal tract or in the central nervous system, or both, remains unclear [2, 3]. There is general agreement that the brain/gut axis is disturbed in IBS, and drugs that modulate this axis theoretically may be able to reduce symptomatology [3].

In patients who fail first line gut directed therapy for IBS, a trial of antidepressant treatment is often considered as a reasonable next step in clinical practice [2, 3]. It is established that the tricyclic antidepressants can slow intestinal transit and therefore may be particularly useful in patients with diarrhea-predominant IBS [4]. Alternatively, the selective serotonin reuptaking inhibitor (SSRI) drug class can accelerate colonic transit [4]; this drug class reduces reuptake of serotonin by the gut serotonin transporter, leading to accumulation of serotonin in the neuroenteric system that can stimulates peristalsis. Therefore, pharmacologically it makes sense to consider targeting patients with constipation predominant IBS using the SSRI drug class. The SSRI's are also often better tolerated than the tricyclic antidepressants, and have anxiety reducing benefits that may also be potentially of value in IBS [5].

In this issue of the Journal, Rahimi et al., report the results of a meta-analysis limited to evaluating the efficacy of SSRI's in IBS; overall, SSRIs were not significantly better than placebo for the relief of individual IBS symptoms [6]. Little data have been published on SSRIs in IBS. Despite a comprehensive search, the authors of this meta-analysis found only five randomized placebo-controlled trials that they could include. This resulted

in a total of just 147 women and 74 men with IBS who were randomized to either an SSRI or placebo. While the available data on SSRI use in IBS is still remarkably limited, the absence of evidence for a benefit does not mean there is no benefit, and looking at the individual trials one could argue the effect generally fell on the side of favouring active therapy over placebo. A type II error (lack of study power) may account for the fact that the pooled analysis failed to detect a significant benefit of SSRIs in IBS [6]. On the other hand, the efficacy of SSRIs for depression has been questioned when both published and unpublished data were recently examined [7]; how much publication bias exists in the IBS field remains speculative, and funnel plots of the data would have been useful to review.

Meta-analysis quality depends on the robustness of the data entered; garbage in, garbage out clearly applies in this field [8]. Although all of the studies in the current meta-analysis reached a sufficient level of quality based on the Jadad score, the small sample size of all of the studies is still of major concern; the randomization process in a small trial is less likely to have taken care of all of the serious unmeasured biases. Interpretation of the current study is further compounded by the fact that when trying to combine the results, there was significant study heterogeneity identified. Unfortunately, study heterogeneity makes pooling of the data problematic and although some authorities still do so, the results need to be viewed with enormous caution [8]. Other methodological issues may also confound interpreting the results. For example, the trials were not large enough to separate out and sub-classify the IBS populations, and therefore whether SSRI's should be reserved for constipation predominant IBS or not is still an unanswered question. The newer antidepressant drugs such as the selective norepinepherine uptake inhibitors (SNRIs) are prescribed in clinical practice and may in particular be useful for neuropathic pain [9]. Whether this drug class has any benefit in IBS has not been tested in randomized controlled trials and objective data are needed.

While the tricyclic antidepressants probably have a greater side-effect profile than the SSRI's, these are still a useful drug class in IBS. Meta-analysis data support their efficacy [10]. It is notable that arguably the best randomized controlled trial failed to show by an intention-to-treat analysis that desipramine (a secondary amine tricyclic) in moderate to full antidepressant doses was superior to placebo in IBS, although the per protocol analysis was suggestive of benefit [11].

A final issue worthy of comment is safety. The adverse event profile was not reported in this meta-analysis, but clearly SSRI's can have several adverse events that must not be forgotten in practice, although reporting of this issue in clinical trials has been inadequate [12]. Side effects of SSRIs can include an increased risk of upper gastrointestinal bleeding, weight loss, reduced libido in both sexes, sleep disturbance, suicidal ideation and rarely the serotonin syndrome. Larger trials with better reporting of both efficacy and safety remain urgently needed in the IBS field.

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